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Impact of *Leuconostoc Mesenteroides* and *Lactobacillus Brevis* on Pro-Inflammatory Cytokines in Rat Models with Chronic Asthma

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Abstract: Allergic asthma is a chronic inflammatory disorder characterized by immune system changes. Allergen inhalation, which causes hyperactivity, eosinophil recruitment, mast cells, and lymphocytes in the upper and lower respiratory tracts, triggers the inflammation cascade and results in local and systemic inflammation responses. However, the mechanism of probiotics in allergic diseases, both in vivo and in vitro, is not fully understood. This research was conducted to observe the effect of single or combined probiotics on the immune system of Sprague Dawley rats. This research used a pre-post-test only control group design. The research was conducted on 30 Sprague Dawley rat models with chronic asthma induced with ovalbumin, divided into 5 groups (NC: negative control; PC: positive control; Lm: *Leuconostoc mesenteriodes*; Lb: *Lactobacillus brevis*; Lm+Lb: a combination of *Leuconostoc mesenteriodes* and *Lactobacillus brevis*). The examinations on eosinophil and neutrophil and IL 17, IL 10, and IL 4 were conducted using the ELISA method. The data were statistically tested using IBM SPSS 25. The administration of single or combined probiotics increased IL-10 ($p < 0.001$) yet decreased IL-17 and IL-4 ($p < 0.001$) in all treatment groups. The results show that using single probiotics, *Leuconostoc mesenterium* best increased IL-10 and decreased IL-17 and IL-4. The dosage administration of single or combined probiotics had a systemic effect on overcoming allergic asthma. In this research, the administration of single probiotics had a better effect when compared with that of combined probiotics.

Keywords: asthma, probiotics, immunomodulator.

肠系膜明串珠菌和短乳杆菌对慢性哮喘大鼠模型促炎细胞因子的影响

摘要：过敏性哮喘是一种以免疫系统改变为特征的慢性炎症性疾病。过敏原吸入会导致上呼吸道和下呼吸道多动、嗜酸性粒细胞募集、肥大细胞和淋巴细胞，引发炎症级联反应并导致局部和全身炎症反应。然而，益生菌在体内和体外在过敏性疾病中的作用机制尚不完全清楚。本研究旨在观察单一或联合益生菌对斯普拉格道利大鼠免疫系统的影响。这项研究使用了一个只有后测的对照组设计。该研究对 30 只卵白蛋白诱导的慢性哮喘斯普拉格道利大鼠模型进行，分为 5 组（阴性对照；阳性对照；肠系膜明串珠菌；短乳杆菌；明串珠菌的组合肠系膜菌和短乳杆菌）。使用酶联免疫吸附测定方法进行嗜酸性粒细胞和中性粒细胞以及白细胞介素 17、白细胞介素 10 和白细胞介素 4 的检查。使用国际商业机器社会科学统计软件包 25 对数据进行统计测试。在所有治疗组中，单一或联合益生菌的施用增加了白细胞介素-10 ($p<0.001$) 但降低了白细胞介素-17 和白细胞介素-4 ($p<0.001$)。结果表明，使用单一益

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生菌，肠系膜明串珠菌最能增加白细胞介素-10 并降低白细胞介素-17 和白细胞介素-4。单一或联合益生菌的剂量给药对克服过敏性哮喘具有全身作用。在本研究中，与联合益生菌相比，单一益生菌的给药效果更好.

关键词：哮喘、益生菌、免疫调节剂。

1. Introduction

Asthma is an allergic disease that is still a health problem because of its effect on reducing the quality of life and requires high costs in its management. World Health Organization (WHO) predicts that asthma patients will increase by 100 million in 2025. Moreover, the per-patient cost will also increase, thus increasing the overall burden of asthma [1]. Allergic asthma is a chronic inflammatory disorder characterized by hyperactivity, recruitment of eosinophils, mast cells, and lymphocytes in the upper and lower airways. All of that triggers an inflammatory cascade and produces a local and systemic inflammatory response [2].

Experimental and clinical data suggest that an imbalance between the responses of T helper 1 (Th1) and T helper 2 (Th2) cells are the basis of an inflammatory allergic process in asthma [3]. Cytokines produced by Th2, such as IL-4, IL-5, IL-9, and IL-13, induce mucus secretion, smooth muscle hyperplasia, subepithelial hypertrophy and fibrosis, secretion of IgE, increased production of T cells-induced chemokines, eosinophils, neutrophils, mast cells, and airway hyperresponsiveness. In contrast, Th1 cytokines, such as IFN-γ, are thought to prevent these processes [4, 5]. In addition, Th17 and T regulatory (Treg) cells play a pro-inflammatory role in developing chronic inflammatory disorders and suppress respiratory tract inflammatory and hyperresponsive responses via IL-17 and IL-10 [6].

Furthermore, a host-microbiota imbalance is a risk factor for allergic disease, and it is also present as a potential component for modification or therapeutic targets in allergic disease [7]. Therefore, probiotics are supplements containing microorganisms that can change the host's microbiota, thereby increasing the innate and adaptive immune response [8].

Recently, there has been enormous evidence of probiotics on asthma. They might regulate macrophages cells, dendritic cells, natural T cells, and killer cells, inducing Treg cells. They also might suppress allergen-induced inflammatory responses [9]. *Leuconostoc mesenteroides* is a probiotic that is quite often used. Several studies have shown the role of this probiotic in increasing body immunity by affecting the Th1-Th2 balance. Another well-known probiotic in treating allergic diseases is *Lactobacillus brevis* which is believed to control allergic responses [10, 11].

However, the mechanism of probiotics in allergic diseases, both in vivo and in vitro, is not fully understood. Therefore, we aimed to assess the effects of *Leuconostoc mesenteroides* and *Lactobacillus brevis* on the immune system in a rat model of chronic asthma.

2. Method

2.1. Research Design

This experimental laboratory research used rats as the experimented animals. The population was divided into 5 groups consisting of 8 samples. Group division and treatment can be seen in Table 1.

Table 1 Group division and treatment

Group	Treatment
(Negative control: NC)	No treatment
(Positive control: PC)	Administered with ovalbumin (OVA) to experience chronic asthma
Treatment group II (G III)	Administered with ovalbumin (OVA) to experience asthma and then also administered with *L. mesenteriodes* orally
Treatment group III (G IV)	Administered with ovalbumin (OVA) to experience asthma and then also administered with *L. brevis* orally
Treatment group IV (G V)	Administered with ovalbumin (OVA) to experience asthma and then also administered with *L. mesenteriodes* + *L. brevis* orally

The rat models with allergic asthma were desensitized on Day-0 and Day-14 with 10 µg of ovalbumin (OVA) per-rat and 1 mg of aluminum hydroxide in 0.5 cc of NaCl 0.9 % per rat in an intraperitoneal manner. From day-21 to day-63, the rats were exposed to 1% of OVA aerosol in NaCl 0.9 % for 30 minutes each three times/week for 6 weeks. Aerosol used nebulizer merk "CompMisk" (model 40-105-000, USA) to the exposure room (27 cm x 20 cm x 9 cm) for each rat group.

Ovalbumin is made of chicken egg white. Ovalbumin is a phosphor-glycoprotein monomer with a 43 – 45 Kd molecular weight. Ovalbumin has been proven to result in asthma in the experimented animals. The ovalbumin used in this research was Sigma Ovalbumin (A5503-1G).

The rats were first adapted in the laboratory for a week. The control group (G I) consisted of 6 rats first separated. The other rats not included in the control group were then desensitized using OVA 10 µg+1 mg alum intraperitoneal on Day-0 and Day-14. Each group of rats was placed in one cage. A day after adaptation, the rats were randomly divided into four groups based on the group divisions' criteria.

The female rats aged 6-8 weeks with the commonly known bodyweight of approximately 200-300 grams were still weighed to ensure that the rats used in this research had approximately 200-300 gr (similar weight). This body weighing was intended to precise the administration of OVA. After the body weighing was performed, the rats were given certain treatments. To cause asthma in rats, they were desensitized with OVA solution in the intraperitoneal manner (i.p) on Day-0 and repeated with the same procedure on Day-14. Then, the exposure with OVA aerosol (through inhalation using a nebulizer) was performed from Day-21 to Day-63. The rats were desensitized with the inhalation of 1 % OVA in normal saline (NaCl 0.9 %) and aerosol for 30 minutes each three times /week for 6 weeks. The treatments to make the rat models with asthma were given to G II, G III, G IV, and G V.

The rats contained in G III were given OVA inhalation and treated with *L. mesenteriodes* orally administered daily right after the OVA exposure process was completed. The rats contained in G IV were given OVA inhalation and treated with *L. brevis* orally administered daily after the OVA exposure process was completed. Finally, the rats in G V were given OVA inhalation and treated with the combination of *L. mesenteriodes* dan *L. brevis* daily after the OVA exposure process was completed.

Twenty-four hours after the rats were nebulized and administered with probiotics (Day- 64), the rats were injected with the intraperitoneal Ketamine 200 µg/g. To measure the serum levels of IL-17, IL-10, and IL-4, an ELISA kit by Elabscience was used.

2.2. Statistical Analysis

Data from the pre- and post-test IL-17, IL-10, and IL-4 were analyzed using the ANOVA (Analysis of variance) test followed by the Post Hoc Test with LSD (Least Significant Difference). In contrast, the analysis of differences in mean levels of IL-17, IL-10, and IL-4 in allergy and treatment groups used paired samples T-test. Statistical test using SPSS for Windows Release 19.0 and $p < 0.05$ was chosen as the minimum significance level.

3. Findings

OVA induction's success in making the rat models with asthma could be revealed by the increasing number of eosinophils and neutrophils on Day-14. The number of eosinophils and neutrophils in the blood of rats induced with OVA in group PC, Lm, Lb, and Lm+Lb was higher when compared with that in NC, which was not induced with OVA (Fig. 1a and 1b).

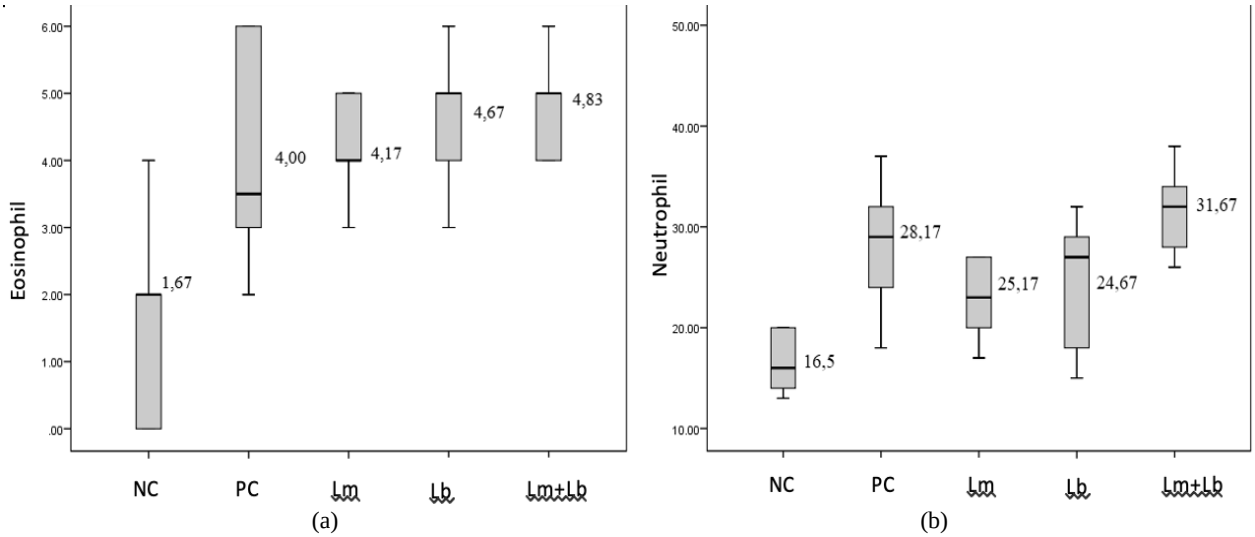

Fig. 1 (a) Mean eosinophil post-induction OVA (PC, Lm, Lb, LM+Lb); (b) Mean neutrophil post-induction OVA (PC, Lm, Lb, LM+Lb)

The increasing number of eosinophils and neutrophils after OVA induction for 14 days indicated

the occurrence of asthma. The statistical testing results show level differences of IL-17, Il-10, and IL-4 in the pre and post-treatments of probiotics Lm, Lb, and Lm+Lb. The levels of IL-17 and IL-4 in groups treated with probiotics (Lm, Lb, and Lm+Lb) were lower and significantly different from the average levels of IL-17 and Il-4 in the group of rats induced with OVA without probiotics administrations (PC) ($p < 0.001$). Based on this result, it was revealed that the administration of probiotics *L. mesenteriodes*, *L. brevis*, and the combination of probiotics *L. mesenteriodes* and *L. brevis* (Lm, Lb, and Lm+Lb) decreased IL-17 and IL-4 belonging to rat models with chronic asthma (Fig. 2, 4).

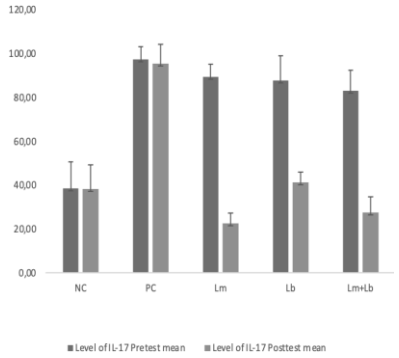

Fig. 2 Level of IL-17

Conversely, the levels of IL-10 belonging to the group treated with probiotics (Lm, Lb, and Lm+Lb) were higher and significantly different from the average level of IL-10 belonging to the groups containing rats induced with OVA without probiotics treatments (PC) ($p < 0.001$). Based on this result, it was revealed that the administration of probiotics *L. mesenteriodes*, *L. brevis*, and a combination of probiotics *L. mesenteriodes* and *L. brevis* (Lm, Lb, and Lm+Lb) increased the IL-10 of rat models with chronic asthma. However, there was no significant difference between the levels of IL-10 and IL-4 ($p > 0.05$) in the treatment groups (Fig. 3, 4).

This result shows that the dosage of single and combined probiotics had the same influence on levels of IL-10 and IL-4. However, this result shows a different level of IL-17 in treatment groups with the lowest average levels of IL-17 belonging to Lm.

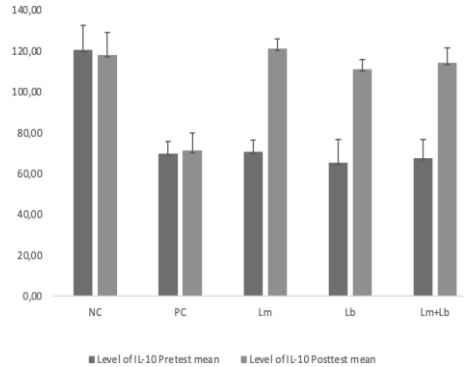

Fig. 3 Level of IL-10

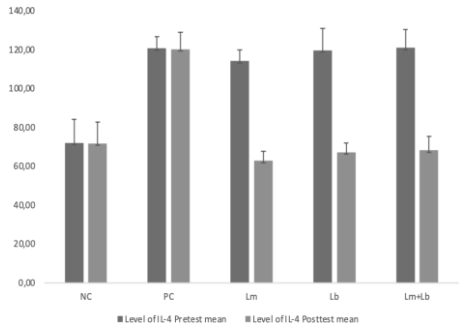

Fig. 4 Level of IL-4

4. Discussion

Asthma is a chronic inflammatory disease known to occur due to the imbalance of Th1/Th2 and Th17 immune responses and is related to dysbiosis. The Th2 responses regulate the inflammation responses involving mast cells, basophil, and eosinophil. In addition, APC cells and lymphocytes interact to increase the Th2 responses to asthma [12]. Th-2 responses have an important role in modulating inflammation through the cytokines of IL-4, IL-5, IL-9, and IL-13 [13, 14]. The increasing IgE, which activates the mucosal mast cells, is characterized by allergic inflammation.[14]. The Th-1 immune responses occur through the transducer signal and transcription-1 (STAT-1) and T-bet activators under the influence of dendritic cells, CD8+ and macrophages resulting in the cytokines of IFN-γ, IL-12, and IL-18.

Interleukin 17 is the cytokine that has an important role in the slow-type reaction triggered by the increasing production of chemokines in some tissues to recruit monocytes and neutrophils to the inflammation side. IL-17 is produced by Th17 cells and induced by IL-23, but when excessive can damage the tissues [15, 16]. Patients with chronic and persistent asthma have slow responses to the corticosteroids, and the number of neutrophils will increase. That is caused by the increasing level of IL-17, which will trigger the neutrophil chemotaxis in the sputum and bronchoalveolar washing fluid of patients with asthma compared to the healthy patients. Interleukin-17 increases the lung tissues, bronchial washing fluid, sputum, and peripheral blood of patients with allergic asthma [16, 17].

Intestinal dysbiosis is the major cause of various inflammation diseases, including asthma. Thus, it is expected that chronic inflammation in chronic asthma and its complications can be well prevented and overcome by overcoming intestinal dysbiosis. However, chronic asthma management is only symptomatic during this time and does not overcome the major problem, that is, intestinal dysbiosis. This research background and literature reviews explain that recently, the compositions of intestinal microbiota belonging to the atopic and healthy babies are different.

Lactobacillus, *Bifidobacterium*, and *Bacteroides spp* in atopic babies have decreased [7]. Therefore, the administration of probiotics can result in different responses depending on the compositions of bacteria used. One effort made for effective management of asthma is by suppressing the inflammation, yet without suppressing impacts on the immune system, which will increase the susceptibility to the viral infection. Thus, it is essential to combine probiotics that have anti-inflammation characteristics and increase the immune system, on the other side, the infectious agent [18].

The results show that the administration of probiotics *L.mesenteriodes*, *L.brevis*, and a combination of *L. mesenteriodes* and *L.brevis* decreased Il-17, and IL-4, yet increased IL-10. The previous research reported that the administration of probiotics *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Streptococcus* were proven to decrease the levels of IL4 and IgE in children with allergic asthma [19]. However, the effect on IL-17, IL-10, and airway remodeling was unknown. Furthermore, some combinations of probiotics, such as *Bifidobacterium longum* and *S. thermophilus*, were known to suppress the production of IL-17. The combination of *S. thermophilus* and *Leuconostoc* strains more strongly triggered the products of cytokine Th1 consisting of IL-12 compared with the probiotics Lactobacillus strains that were recently used clinically [20]. In addition, it was known that the administration of L. brevis HY7401 increased the cytokine Th1 and decreased cytokine Th2, IgE production [11]. That underlies the selection of bacterial strains *Leuconostoc mesenteriodes (L. mesenteriodes)* and *Lactobacillus brevis (L. brevis)* in this research.

*Leuconostoc mesenteri*es result from bacteria fermentation that can produce bacteriocin and live in the extensive pH range due to the organic acid contained in bacteria. The bacteria in LAB (Lactic Acid Bacteria) have exopolysaccharide (EPS) on their cell walls. EPS in *Leuconostoc mesenteriodes* modulates the systemic and local immune responses binding the LPS TLR-4 agonist modulating the inflammation response in the intestinal mucosa. The TLR4 activation can give an anti-inflammation effect and immunoregulator [21]. *Lactobacillus brevis* is lactate acid in rod-shaped, gram-positive bacteria with 16 different strains. Both *L. mesenteriodes* and *L. brevis* can be found in fermented food, such as *asinan* (salted vegetables or fruits) and *acar (*pickles*). L. brevis* is a normal intestinal flora within the humans' intestines, vagina, and fesses [22].

There were some limitations in this research: 1. This research did not observe how prebiotic administrations impact the intestinal mucosa's immune system parameters and their relationships locally and systematically; 2. No culture was made to determine whether or not the administered probiotics influenced the growth in the intestines, and no further gene-sequencing was performed.

5. Conclusion

Based on the research results, it can be concluded that the combined probiotics of *L. Mesenteriodes* and *L.Brevis* influenced the immune system of rat models with chronic asthma. Furthermore, the influence of immunomodulation on the immune system was revealed from some parameters showing the equal immune responses of Th1/Th2, Treg, and Th17 which increased IL-10 and IFN- γ, yet decreased IL-17, IL-4, and IgE. Furthermore, the dosage of single *L. mesenteriodes* and *L. Brevis* and their combination show the same results.

The novelty of our study is the use Sprague Dawley rats model, as the previous studies using mice. Our results showed that the administration of probiotics L. mesenteriodes and L. brevis either alone or in combination can reduce IL-17, IL-4, and IgE and increase IL-10, thus improving airway remodeling in the bronchi.

This study has 4 limitations, and it did not observe the impact of probiotic administration on the parameters of the immune system in the intestinal mucosa and its relationship locally and systemically. Second, no culture was performed to determine whether the probiotics had grown in the intestines, and no next gene sequencing was performed. Next, there are differences in systemic and local effects on the administration of probiotics in Sprague Dawley because the dose used refers to the dose of Balb/C mice. Last, there was no ovalbumin-induced group before treatment with inactivated probiotics to compare the local effect in the pulmonary bronchi before and after treatment with probiotics.

Based on its limitation, we suggest further research investigating the impact of probiotic administration on immune system parameters in the intestinal mucosa and its association locally and systemically. Second, perform microbiota culture in the digestive tract to determine the presence of growth and perform next gene sequencing. Then a study using Sprague Dawley rats as chronic asthma model rats is necessary to adjust the dose of probiotic administration. Last it is necessary to have an ovalbumin-induced group before treatment with inactivated probiotics to compare the local effect in the pulmonary bronchi before and after probiotics for further research.

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